DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on March 4, 2008, has been entered.

1. The amendment filed March 4, 2008, is acknowledged and has been entered in part.

2. The amendment filed March 25, 2008, is acknowledged and has been entered. Claims 79 and 88 have been canceled. Claims 78, 80-84, 86, 87, and 89-93 have been amended.

3. Claims 78, 80-84, 86, 87, and 89-94 are pending in the application and are currently under prosecution.

Response to Amendment

4. In response to the amendment filed March 4, 2008, the amendment to the specification at page 1 is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is: "The entire text of U.S. Patent Application Serial No. 09/662,270, [and] U.S. Patent Application Serial No. 09/097,199 (now U.S. Patent No. 6,218,529) [...] is specifically incorporated herein by reference". An incorporation-by-reference statement added after the filing date of an application is not permitted

because no new matter can be added to an application after its filing date. See 35 U.S.C. § 132(a). When a benefit claim is submitted after the filing of an application, the reference to the prior application cannot include an incorporation-by-reference statement of the prior application. As originally filed, the specification recited:

> The present application is a continuation-in-part of co-pending U.S. Patent Application Serial No. 08/692,787 filed July 31, 1996. The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer.

A preliminary amendment filed on the same date as the application amended this paragraph to recite:

> This application claims priority to co-pending patent application, Serial No. 09/662,270, filed on September 14, 2000, which is a divisional application of U.S. Serial No. 09/097,199, which issued as U.S. Patent 6,218,529 on April 17, 2001. The present application is a continuation-in-part of co-pending U.S. Patent Application Serial No. 08/692,787 filed July 31, 1996. The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer.

This statement of incorporation, which is present in the originally filed application, appears to refer to only a single disclosure, namely that of U.S. Patent Application Serial No. 08/692,787; it does not appear to reference more than one disclosure, or more particularly it does not appear to include reference to the disclosures of Application Serial No. 09/662,270 or Application Serial No. 09/097,199.

Notably, too, there appears no mention of any intent to incorporate by reference into the present application the disclosures of either Application Serial No. 09/662,270 or Application Serial No. 09/097,199 on the Transmittal (i.e., Request for Filing Divisional Application, as filed October 10, 2001).

Therefore, the incorporation-by-reference statement in the amendment to the specification introduces new matter and renders the amendment improper. See *Dart Industries v. Banner*, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). See 1268 OG 89 (18 March 2003).

Applicant is required to cancel the new matter in the reply to this Office Action, or to rebut the Office's position.

Priority

5. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of Application No. 09/662,270, filed September 14, 2000, which claims benefit of Application 09/097,199, filed June 12, 1998, which claims benefit of Application No. 08/692,787, filed July 31, 1996, which claims benefit of Provisional Application No. 60/001,655, filed July 31, 1995, and Provisional Application No. 60/013,611, filed January 11, 1996, is acknowledged.

However, claims 78, 80-84, 86, 87, and 89-94 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

In addition, since claims 78, 80-84, 86, 87, and 89-94 are presently drawn to a method for treating breast or bladder cancer, it is aptly noted that while the specification of U.S. Patent Application No. 08/692,787 describes treating prostate cancer by a process comprising administering to a patient an agent that binds to and/or inhibits the activity of a polypeptide encoded by a nucleic acid molecule corresponding to the marker designated UC Band #28 (i.e., SEQ ID NO: 3), it does not describe such processes for treating breast or bladder cancer; moreover, the specification does not appear to teach or suggest the presence, or more particularly the over-expression of the gene corresponding to this marker in either breast or bladder cancer. Accordingly, the

specification of U.S. Patent Application No. 08/692,787 fails to adequately describe the presently claimed invention, so as to satisfy the written description and enablement requirements set forth under 35 U.S.C. § 112, first paragraph.

Accordingly, the effective filing date of claims 78, 80-84, 86, 87, and 89-94 is deemed the filing date of U.S. Patent Application No. 09/097,199, namely June 12, 1998.

Grounds of Objection

Specification

6. The specification is objected to because of disclosures by the impermissible referral to embedded hyperlinks and/or other forms of browser-executable code, and to the Internet contents so identified.

Reference to hyperlinks and/or other forms of browser-executable code, and thus to the Internet contents so identified, *is impermissible and therefore requires deletion*.

At page 6 of the amendment filed March 4, 2008, Applicant has amended the specification to delete "www" from the disclosure at page 119, beginning in line 8; however, the specification still contains a reference to the information contained on an Internet (World Wide Web) website, namely "cancer.org/statistics/98cff/98prosta.html".

As previously explained, even if the link is "inactivated", the disclosure still refers to the website, and to the Internet contents so identified.

Notably, another example of such an impermissible reference appears in the specification at page 117, line 20.

Again, the attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code, for example, (i.e., any reference to the contents of an Internet website) is considered to be an improper incorporation by reference and requires deletion.

By way of further explanation, M.P.E.P. § 608.01(p) does **not** provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) U.S. patents and pending U.S. applications, or

patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates material by reference, or (4) a foreign application. Non-essential information may be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned U.S. applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code, because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained in a website will always remain useful the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 U.S.C. § 112, first and second paragraphs. As such, recitation of such references is not permitted.

A hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases referred to by such disclosures to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, or to provide antecedent basis for the subject matter of claims in the instant application or related applications, and if the

material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See M.P.E.P. § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Grounds of Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 78, 80-84, 86, 87, and 89-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 78, 80-84, 86, 87, and 89-94 are vague and indefinite for the following reasons:

Claims 78 and 87 recite the phrase "effective amount" without making clear what effect is necessarily achieved by the amount.

The metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained, where the claims recite the phrase "effective amount", yet fail to state the function that is necessarily achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

Claims 78, 80-84, and 86, as originally presented for prosecution on the merits, and drawn to the subject matter of the elected invention, recited a method of treating a patient with cancer comprising administering to the patient an agent that inhibits a peptide or polypeptide encoded by SEQ ID NO: 83 or a fragment thereof or that inhibits a peptide or polypeptide encoded by SEQ ID NO: 85 or a fragment thereof.

Claims 87 and 89-94, as originally presented for prosecution on the merits, and drawn to the subject matter of the elected invention, recited a method of treating a cancer cell comprising administering to the cell an agent that inhibits a peptide or polypeptide encoded by SEQ ID NO: 83 or a fragment thereof or that inhibits a peptide or polypeptide encoded by SEQ ID NO: 85 or a fragment thereof.

As presently amended, claims 78, 80-84, and 86 are drawn to a method of treating a patient with breast cancer, bladder cancer or prostate cancer comprising administering to the patient an effective amount of agent that binds to a peptide or polypeptide encoded by SEQ ID NO: 83, a fragment thereof, SEQ ID NO: 85, or a fragment thereof; and claims 87, and 89-94 are drawn to a method of treating a breast cancer, bladder cancer or prostate cancer cell comprising administering to the cell an effective amount of agent that binds to a peptide or polypeptide encoded by SEQ ID NO: 83, a fragment thereof, SEQ ID NO: 85, or a fragment thereof.

It does not appear that the specification expressly defines the term "effective amount" in the context of the claim language[1].

At paragraph [0031], for example, of the published application, the specification discloses: "the present invention encompasses methods for treating breast or bladder cancer patients by administration of effective amounts of antibodies specific for the

[1] The term "imaging effective amount" is defined at paragraph [0190] of the published application (i.e., U.S. Patent Application Publication No. 2003/0050470-A1), but the therapeutically effective amount of the antibody is not.

peptide products of breast or bladder cancer markers identified herein, or by administration of effective amounts of vectors producing anti-sense messenger RNAs that bind to the nucleic acid products of breast or bladder cancer markers, thereby inhibiting expression of the protein products of breast or bladder cancer marker genes". While this disclosure makes evident that the amount of the vector producing an anti-sense mRNA is effective to inhibit expression of the protein products encoded by the genes, it does not make clear what effect the antibody that binds to the peptide products must have.

So, in this instance, it cannot be ascertained whether the amount of the antibody that binds to the peptide or polypeptide is an amount that is necessarily effective to inhibit the peptide or polypeptide, as in accordance with the subject matter of the elected invention, an amount that is necessarily effective to be therapeutic, perhaps an amount that is effective to bind to the peptide or polypeptide, or an amount that is effective to bind to cancer cells that express the peptide or polypeptide.

Then, too, because the claims recite the method treats *a patient* with cancer, and not the cancer that afflicts the patient, it is questionable as to what objective or purpose the practice of the claimed invention is to have.

If the amount of the antibody is considered an amount that is effective to be therapeutic, it is unclear what function the antibody is required to have when therapeutically administered to the patient. Moreover, it is unclear what therapeutic effect the claims require the "effective amount" of the antibody to be sufficient to achieve[2].

Notably, the various endpoints and extents that define effective treatment are of a more conditional or qualitative nature. So, while the effective amounts of the antibody might be amounts thereof that are necessary to *treat* cancer in a patient, it is still not immediately evident what *therapeutic effect* is necessarily achieved. The therapeutically effective amount might be palliative, or it might be curative; it might be sufficient to achieve disease remission, or it might be merely sufficient to slow the

[2] See *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 79 USPQ2d 1705 (Fed. Cir. 2006), which is of relevance.

growth and/or spread of the cancer. It is submitted that the expected or desired effect that is to be achieved in the practice of the claimed invention to treat cancer, unless more particularly defined, is highly subjective and would tend to vary substantially.

If, for example, the growth or survival of the cancer cell is necessarily inhibited by the effective amount of the antibody, as opposed to, say, the activity of the peptide or polypeptide, it is entirely possible that an amount of an antibody that effectively inhibits the peptide or polypeptide *in vitro* may be insufficient to inhibit the growth or survival of the cancer cells *in vivo*. So, depending upon the actual effect that might be achieved by the claimed amount of the antibody that binds the peptide or polypeptide, if not clearly and particularly pointed out, it is expected that the metes and bounds of the subject matter that is encompassed by the claims may vary rather substantially.

Not inconsistently with this viewpoint, the specification merely discloses at paragraph [0319], for example, that "[an] effective amount of the therapeutic composition is determined based on the intended goal" and that "[the] quantity to be administered, both according to number of treatments and unit dose, depends on the protection desired." Such a vague description of the effect that is necessarily achieved by the effective amount of the therapeutic composition comprising the antibody that binds to the peptide or polypeptide would not permit the artisan to know or determine what effect must be achieved by the claimed effective amount of the antibody in practicing the process that is considered by Applicant as the invention, but serve to highlight the fact that the metes and bounds of the subject matter encompassed by the claims cannot be unambiguously known or determined, and might only be surmised subjectively.

However, in accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is

> covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

Therefore, because the claims fail to delineate with the requisite clarity and particularity the metes and bounds of the subject matter that Applicant regards as the invention, so as to permit the skilled artisan to know or determine infringing subject matter, the requirement set forth under 35 U.S.C. § 112, second paragraph, has not been met.

Applicant's arguments set forth in the amendment filed March 4, 2008, beginning at page 20, have been carefully considered but not found persuasive for these reasons.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 78, 80-84, 86, 87, and 89-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001;

hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a method of treating a patient with breast, bladder or prostate cancer, said method comprising administering to the patient an effective amount of an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83 or a fragment thereof, or that binds to a peptide or polypeptide encoded by SEQ ID NO: 85 or a fragment thereof.

For the reasons set forth in the Examiner's Answer to the Appeal Brief filed October 16, 2006, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Applicant has since amended the claims such that the "agent" that inhibits the peptide or polypeptide to which the claims are directed is an antibody that binds to the peptide or polypeptide.

At page 13 of the amendment filed March 4, 2008, Applicant summarizes their arguments traversing the propriety of maintaining this ground of rejection in light of their amendment, remarking that "[the] variety of types of antibodies described in the specification, in combination with their common ability to bind to SEQ ID NOs: 83 and 85 and the descriptions of other characteristics of this genus, demonstrate that the inventors were in possession of the claimed genus at the time the application was filed" (page 13, paragraph 3).

In response, the Examiner disagrees.

To begin with the claims are directed to an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83, or a fragment thereof, or SEQ ID NO: 85, or a fragment thereof – the claims are not drawn to a genus of antibodies that have a "common ability to bind to SEQ ID NOs: 83 and 85". SEQ ID NO: 83 and SEQ ID NO: 85 are DNA sequences.

Then, presuming that Applicant did not actually intend to argue that the claims are directed to antibody that bind to the DNA sequences of SEQ ID NO: 83, or a fragment thereof, or SEQ ID NO: 85, or a fragment thereof, it is aptly noted that the

claims are not directed to an antibody that binds to a well characterized peptide or polypeptide, but rather to an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83, or a fragment thereof, or SEQ ID NO: 85 or a fragment thereof.

Which peptide or polypeptide is this?

It is not necessarily a peptide or polypeptide comprising the amino acid sequence of SEQ ID NO: 84 or SEQ ID NO: 86.

In fact, according to the claims, it might be a peptide or polypeptide comprising as few as one or two contiguous amino acids (i.e., a fragment) of the amino acid sequence of SEQ ID NO: 84 or SEQ ID NO: 86; or it might be a peptide or polypeptide that is encoded by one or another opening reading frame of which the DNA sequences of SEQ ID NO: 83, or a fragment thereof, or SEQ ID NO: 85, or a fragment thereof, are comprised.

The peptide or polypeptide that is encoded by a fragment of SEQ ID NO: 83 or SEQ ID NO: 85 is not necessarily expressed by breast, bladder or prostate cancer cells; it is not necessarily a peptide or polypeptide that is expressed at the surface of any cell, but might rather be a secreted peptide or polypeptide.

Alternatively, the peptide or polypeptide encoded by a fragment of SEQ ID NO: 83 or SEQ ID NO: 85 might be a peptide or polypeptide that is localized to the cytoplasm or nucleus of a cell, and which in general is not accessible to the antibody that binds to the peptide or polypeptide after it is administered to the patient.

Though the specification describes the polypeptides of SEQ ID NO: 84 and SEQ ID NO: 86, neither is fairly considered representative of the genus of peptides and polypeptides, as a whole, which are encoded by SEQ ID NO: 83, or a fragment thereof, or SEQ ID NO: 85 or a fragment thereof. This is because the genus of peptides and polypeptides include members having widely varying structures and functions, which do not necessarily share any particularly identifying structural or functional features with the polypeptides of SEQ ID NO: 84 or SEQ ID NO: 86.

Thus, the claims are not directed to an antibody or a plurality of antibodies that bind to any one well characterized peptide or polypeptide, but are instead antibodies

that bind to any of a genus of structurally and functionally disparate peptide and polypeptides encoded by at least a portion of SEQ ID NO: 83 or SEQ ID NO: 85.

However, the particular identities of the peptides or polypeptides to which the antibody binds is not the sole issue here, since the claims are directed not directed to an antibody, per se, but rather to a process of treating that utilizes that antibody; as such, the antibody must not only bind to the peptide or polypeptide, but must also be effective to treat "a patient with breast cancer, bladder cancer or prostate cancer".

Here, it is merely presumed that the antibody must be effective to treat the disease that afflicts the patient, not just the patient, but as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, it cannot be ascertained what actual effect the amount of the antibody administered to the patient must achieve.

So, if the antibody must treat breast cancer, bladder cancer or prostate cancer, it stands to reason that the antibody must affect the growth and/or survival of the cancer cells in the patient.

While it might be expected that an antibody that is conjugated to a cytotoxic agent (e.g., a radioisotope or chemotherapeutic drug) would inhibit the growth and/or survival of cancer cells in a patient, as explained in the Examiner's Answer, the claims are not so limited.

Instead, the genus of “antibodies” includes, for example, naked antibodies that bind the polypeptide and inhibits its specific activity or function, so as to inhibit the growth and/or survival of the cancer cell expressing that polypeptide.

Notably, too, the genus of "antibodies" includes not just monoclonal antibodies, but also polyclonal antibodies, which the prior art teaches lack the specificity necessary to achieve therapeutic efficacy in treating diseases, such as cancer.

Then, regardless of whether the antibody is a monoclonal antibody or not, and regardless of whether or not the antibody is conjugated to a cytotoxic moiety or not, if the peptide or polypeptide encoded by at least a portion of SEQ ID NO: 83 or SEQ ID NO: 85 is not displayed at the surface of breast, bladder and prostate cancer cells, and then at a level that exceeds the level it is displayed by other cells (i.e., normal, non-

cancerous cells), the antibody will not selectively target or bind to those cells after it is administered to the patient (or to the cell).

As has been explained at length in preceding Office actions, it is not evident that even the polypeptides of SEQ ID NO: 84 and SEQ ID NO: 85 are displayed at the surface of cells; moreover, it is not evident that the gene encoding these polypeptides is more highly expressed by breast, bladder and prostate cancer cells, as compared to normal breast, bladder and prostate cancer cells, for example.

At page 13 of the amendment filed March 4, 2008, Applicant has argued that relevant, identifying features of the genus of antibodies to which the claims are directed includes their application in diagnostics; it is however not understood how an antibody that is diagnostically useful might reasonably be expected to be therapeutically useful to treat breast cancer, bladder cancer, or prostate cancer. The antibody that is used diagnostically is not necessarily an antibody that inhibits the function or activity of a peptide or polypeptide encoded by at least a portion of SEQ ID NO: 83 or SEQ ID NO: 85, nor is it necessarily an antibody that inhibits the growth and/or survival of breast, bladder, and prostate cancer cells.

Then, as explained in preceding Office actions, although the specification describes the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 as novel (page 111, Table 3), it does not disclose the specific activities or functions of the polypeptides encoded by these nucleotide sequences, which are inhibited by members of the genus of "antibodies" that bind to the polypeptides, so as to inhibit the growth and/or survival of breast, bladder and prostate cancer cells. Consequently, as further explained in preceding Office actions, the skilled artisan cannot envision such antibodies, which are inhibitors of an activity or function that has not been described, nor could the skilled artisan distinguish an antibody capable of inhibiting the activity or function in the absence of such a description. Therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Again, an antibody that binds the polypeptide may not inhibit its function, as the antibody may be agonist or otherwise, the antibody may not affect the activity of the

polypeptide. Only an antibody that binds the polypeptide, *which is conjugated to a radionuclide or chemotherapeutic agent*, could be immediately envisioned, given the otherwise inadequate disclosure of the claimed invention.

However, because a specific function or activity of the peptide or polypeptide encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85, or fragments thereof, has not been described, the skilled artisan could not envision, recognize, or distinguish an antibody that binds to the peptide or polypeptide and inhibits it activity or function, so as to be therapeutically effective in treating breast, bladder, or prostate cancer in a patient.

Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of antibodies that bind the polypeptide and inhibit its activity or function, so as to provide therapeutic benefit. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, the claims are not solely directed to an antibody that binds a well-characterized molecular target, but rather to a naked antibody that binds a polypeptide and inhibits its activity or function, so as to be therapeutically effective; and yet, the specification fails to describe the activity or function of the polypeptide. The specification fails to describe an antibody that binds the polypeptide to specifically inhibit its activity or function; and it fails to describe an antibody not

conjugated to a radionuclide or chemotherapeutic agent, which inhibits the progression of breast, bladder or prostate cancer. Moreover, it fails to describe the "epitope" of the polypeptide to which such an inhibitory antibody must bind.

There is factual evidence that the detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen. For example, Stancoviski et al. (of record) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1).

By way of explanation, Jiang et al. (of record) teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2.

Such factual evidence indicates that the detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen.

In fact, the prior art pointedly teaches the skilled artisan cannot predict the effect of an antibody upon the growth of cancer cells, since it is well understood that antibodies binding the same antigen, or even the same epitope of an antigen, may have strikingly different effects.

With regard to the written description requirement, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed, there is

in fact such unpredictability in this instance, especially since it is not evident that either the polypeptides of SEQ ID NO: 84 or SEQ ID NO: 85 are expressed at the surface of breast, bladder and prostate cancer cells, and then at a concentration that exceeds their level of expression at the surface of normal, non-cancerous cells, and furthermore because it cannot be predicted whether a naked antibody that binds to the peptide or polypeptide, if displayed at the surface of the cancer cells, will have an inhibitory effect upon the cells' growth and/or survival.

This position is further supported by De Santes et al. (*Cancer Res.* 1992 Apr 1; **52**: 1916-1923). Des Santes et al. teaches administering radiolabeled anti-ErbB2 (Her-2/*neu*) monoclonal antibody 4D5 to a subject caused a marked inhibition of tumor growth in the subject; however, the unlabeled, naked antibody had no effect on tumor progression; see entire document (e.g., the abstract; page 1921, Figure 7). Again, as indicated above, unless the antibody or antigen binding portion thereof is conjugated to a cytotoxic drug or prodrug, the prior art teaches it cannot be determined *a priori* whether an antibody is capable of inhibiting the growth of cancer cells, or more particularly, whether it is used effectively to treat prostate cancer. Moreover, the prior art teaches the effectiveness of an antibody is necessarily determined empirically; and then, given the lack of clarity and particularity with which the specification describes the claimed process, it is submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

It follows from the above discussion of the related prior art that the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on neoplastic cells and inhibit the growth of those neoplastic cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of neoplastic cells).

In further support of this position, Boyer et al. (*Int. J. Cancer.* 1999; **82**: 525-531) teaches different epitopes of a tumor-associated antigen (i.e., Her-2) can serve as distinct targets for immunotoxins; see entire document (e.g., the abstract). Boyer et al. teaches a panel of antibodies conjugated to a cytotoxic moiety, which bind to discrete epitopes, produced markedly different cytotoxic effects that did not correlate with the isotype of the antibody, its binding affinity, the relative position of its epitope, or its internalization by the targeted cells; see, e.g., the abstract. Similar epitopic-dependency has been described by Press et al. (*J. Immunol.* 1988 Dec 15; **141** (12): 4410-4417); ricin A-chain comprising immunotoxins directed against different epitopes of an antigen differ markedly in their ability to kill the targeted cells (see entire document, e.g., the abstract). Then, too, Bettler et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Sep; **86** (18): 7118-7122) teaches an anti-CD23 antibody, which is designated MHM6 promotes, as opposed to inhibits the growth of B cells expressing CD23; see entire document (e.g., the abstract; page 7121, column 2; and page 7122, paragraph bridging columns). MHM6 does not inhibit binding of IgE to the receptor, whereas other anti-CD23 antibodies described Bettler et al., which presumably bind discrete epitopes of CD23, are capable of doing so; see, e.g., page 7121, column 2.

Indeed, Riemer et al. (*Mol. Immunol.* 2005; 42: 1121-1124) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

Notably, since the peptide or polypeptide to which the claimed antibody binds has not been described with clarity and particularity, it follows that the epitope of the peptide or polypeptide that is recognized by an antibody that binds to the peptide or polypeptide expressed by cancer cells, so as to thereby inhibit the growth and/or survival of those cells, is not known, has not been characterized, and/or is not described in the specification.

Nevertheless, it is aptly noted that even if an antibody were to bind to an overlapping epitope, as opposed to the same epitope recognized by an antibody that

binds to and inhibits the growth of the cancer cells, the prior art teaches the skilled artisan cannot predict whether the antibody, even when conjugated to a cytotoxic moiety, can be used effectively to treat cancer.

This position is supported by the teachings of Pettersen et al. (*J. Immunol.* 1999 Jun 15; **162** (12): 7031-7040). Pettersen et al. teaches anti-hIAP (CD47) monoclonal antibodies Ad22 and 1F7, which induce apoptosis of Jurkat T cells and peripheral blood mononuclear cells (PBMC) expressing the antigen to which these antibodies bind; but Pettersen et al. also teaches other antibodies, namely monoclonal antibodies 2D3 and B6H12 that commonly bind to hIAP/CD47, which *do not induce apoptosis* of the cells to which it binds; see entire document (e.g., the abstract; and page 7033, column 1). As might be expected, given the recognized epitope-dependency of the various effects caused by different antibodies binding the same antigen, Pettersen et al. teaches monoclonal antibody 2D3 and Ad22 bind discrete epitopes; but curiously Pettersen et al. teaches monoclonal antibody B6H12, despite its apparent inability to induce apoptosis, binds an epitope that overlaps the epitopes to which monoclonal antibodies Ad22 and 1F7 (see, e.g., page 7032, column 2). Similarly, Bernard et al. (*Human Immunol.* 1986; **17**: 388-405) describes differential effects by antibodies binding "competing" antigenic sites or epitopes. Thus, the prior art suggests that a genus of antibodies capable of causing a desired effect (e.g., the induction of apoptosis) is not adequately described with the requisite clarity and particularity by a mere description of a species falling within that genus; and as such, it is submitted the claimed invention could not be practiced, as of the filing date sought by Applicant, without empirically determining whether or not any given antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83, SEQ ID NO: 85, or a fragment of either sequence might be used effectively to treat a neoplastic disorder and achieve the claimed objective of the invention.

Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision,

recognize, or distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells).

Applicant is again reminded that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Furthermore, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to specifically bind a polypeptide and inhibit its activity, or the ability to bind a cancer cell and inhibit its growth or metastatic progression, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the "agents" (e.g., naked antibodies that bind the

polypeptide and inhibit its activity, so as to be therapeutically effective) to which the claims are directed, it is impossible to use the claimed invention.

In addition, although the skilled artisan could potentially screen candidate antibodies that bind to the peptide or polypeptide to identify those that inhibit function of the peptide or polypeptide, and/or inhibit the growth or survival of cancer cells expressing the peptide or polypeptide, so as to be therapeutically effective in treating breast, bladder or prostate cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Thus, while Applicant's arguments traversing this ground of rejection have been carefully considered, they have not been found persuasive, as the disclosure fails to satisfy the "written description" requirement set forth under 35 U.S.C. § 112, first paragraph.

11. Claims 78, 80-84, 86, 87, and 89-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242

> U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Careful consideration of these factors indicates that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the "written description" rejection above, the claims are drawn to a method of treating a patient with breast, bladder, or prostate cancer, said method comprising administering a member of a genus of "antibodies" that bind to a peptide or polypeptide encoded by at least a fragment of the polynucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85. If it is presumed that the claimed invention is intended to treat the disease, not just the patient afflicted by the disease, then it might also be presumed that the amount of the antibody that is administered to the patient must be therapeutically effective to reduce the growth and/or survival of the cancer cells in the patient. While the antibody that binds the peptide or polypeptide might be conjugated to a radionuclide or chemotherapeutic agent, the genus of antibodies includes antibodies

that are not conjugated to such cytotoxic moieties (i.e., "naked" antibodies), which should act to inhibit the peptide or polypeptide, as would be consistent with Applicant's election in response to the restriction requirement.

As explained in preceding Office actions, although the specification describes SEQ ID NO: 83 and SEQ ID NO: 85 as novel (see, e.g., page 111, Table 3, of the specification, as filed), it does not teach the specific activity or function of the polypeptide encoded by these nucleic acid sequences. Because the function or activity of the polypeptide is not disclosed, the skilled artisan could not use the claimed invention without first having to perform undue and unreasonable additional experimentation to first determine the function or activity of the protein, secondly to determine whether the function or activity of the protein correlates with the onset or progression of cancer, and if so, then to design or discover a compound that inhibits that function or activity, which can be used in practicing the claimed invention to treat breast, bladder or prostate cancer.

Although the specification asserts it is possible to predict protein function, in some cases, from primary sequence data, provided that sequence homology exists between the unknown protein and a protein of similar sequence and known function, in this instance, the specification does not disclose whether the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85 bear any significant and substantial homology to other proteins of known functions and activities. Given the fact that the structures and functions of the peptide or polypeptide to which the antibody binds vary rather substantially, it is unreasonably expected that most are expressed by cancer cells, or that most will have any association with the growth or survival of cancer cells. Moreover, as evidenced by Skolnick et al. (of record), for example, the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate. Thus, contrary to the assertions set forth in the instant disclosure, the skilled artisan cannot reliably and accurately predict the function of a novel protein upon the basis of only an observed similarity in its amino acid sequence and those of other proteins having known functions.

In fact, the specification, itself, supports this very position, since it discloses, "Inhibitors could also potentially be designed for the previously unreported prostate, bladder or breast cancer-markers identified in the present invention [but this] is complicated by the fact that no specific function has been identified for most of these gene products, and no data is available on their three-dimensional structures" (page 71, lines 1-6).

It was further noted in preceding Office actions that even if the function or activity of the polypeptide were known, the skilled artisan could still not use the claimed invention without first having to perform undue and unreasonable experimentation, because the specification does not teach the skilled artisan to make an inhibitor of the polypeptide, which, in particular, can be used in practicing the claimed invention to treat cancer. Additionally, even though cancer cells may overexpress the protein, its function or activity may not be associated with the onset or progression of cancer; therefore, an inhibitor of the polypeptide may not inhibit the onset or progression of cancer in the patient and would therefore not provide an effective treatment of cancer. Consequently, before designing or striving to discover an inhibitor of the protein, the skilled artisan would have to determine if such an inhibitor might be therapeutically valuable.

Inasmuch as the claims are directed to antibodies, as explained in "written description" rejection above, not all antibodies are reasonably expected to be capable of inhibiting the activity and function of the polypeptide. Other antibodies may not have any effect upon its activity or function, whereas some antibodies may actually act as agonists, promoting or enhancing its activity or function, rather than inhibiting the polypeptide.

Claims 83 and 92 are directed to antibodies that bind the polypeptide, which are conjugated to a radionuclide. In general, an antibody that binds selectively to a cancer cell, which is conjugated to a radionuclide, may be used to treat the disease, since it provides exposure to the radioactivity, which is toxic to the cells. However, as explained in preceding Office actions, while the specification teaches the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), the specification does not actually teach whether the protein is expressed at the surface of

the cells. If the inhibitor is an antibody or another type of inhibitor that binds directly to the polypeptide, and the polypeptide is not expressed at the surface of the targeted cancer cells, the antibody or other inhibitor cannot specifically bind those cells and therefore will have no specific inhibitory effect upon those cells. As further noted in preceding Office actions, it is believed that An et al. (of record) provides factual evidence that the protein, which is designated therein as UROC28, is not expressed at the surface of cells. An et al. teaches immunohistochemical analyses of glandular epithelial cells of prostate and breast cancers revealed the protein localizes in the nucleus and cytoplasm; see entire document, particularly page 7018, Figure 5.

Applicant has previously provided a copy of a declaration under 37 C.F.R. § 1.132 by Dr. Veltri, which was filed during prosecution of a copending, related application (i.e., U.S. Patent Application No. 09/966,762). Applicant has argued that this declaration provides factual evidence that the polypeptide (i.e., UROC28), or at least a portion thereof, is present at the extracellular surface of prostate cancer cells.

The merit of the declaration filed in the copending application has been carefully considered to the extent that it is believed to be applicable to the issues raised herein.

Dr. Veltri has suggested that An et al. does not teach the protein was *not* expressed as an extracellular, plasma membrane-associated, or trans-membrane protein, only that it was *primarily* localized in the cytoplasm (i.e., the inside of the cell) and more particularly, to at least some extent, in the nucleus; see item #7 at page 3. Agreeably, An et al. does not teach that the protein, or a portion thereof, was *not* exposed at the cell's extracellular surface; but, if it was, its presence or level of expression at the extracellular surface must not have been remarkable.

The declaration states, "the present specification discloses [...] a significant of UC28 localizes to the cell membrane" (item #9 at page 3). There is, however, no factual evidence attached to the declaration to support this assertion. As explained in preceding Office actions, while the instant specification teaches the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), the specification does not actually teach whether the protein is expressed at the surface of the cells. Given the methodology and resolution of the microscopy used by An et al. it is

submitted that it would not be possible to reasonably conclude that the protein is exposed at the surface of the cell; if such, methodology was used by Applicant to determine that the protein is "mainly on the cell membrane", it is further submitted that, using such methodology, one could not reliably distinguish a protein that is localized on the inside surface of the plasma membrane from a protein that is localized in the cytoplasm, or a protein that is transmembrane protein. Because the tissue sections used in the process are fixed and permeabilized, the antibody is capable of binding antigens both inside and out. Furthermore, the antibody that was used was a polyclonal antibody, so it recognizes many different antigenic determinants on the protein, not just antigenic determinants present on a putative extracellular domain; therefore, at the resolution used, it would not be possible to determine with any degree of certainty whether the protein is exposed at the surface of living cells.

The specification the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), but as evidenced by Maddala et al. (of record), for example, not all proteins that appear localized "mainly on the cell membrane" are transmembrane proteins comprising an extracellular domain that is accessible to an antibody at the outside surface of the cell; see entire document (e.g., the abstract). Maddala et al. teaches localization of α-crystallin, an intracellular protein, to the leading edges of the plasma membrane of lens epithelial cells; see, e.g., the abstract. This protein associates with the plasma membrane, but it is not a transmembrane protein. Using the methodology exemplified by An et al., how might one distinguish a protein, such as α-crystallin from a transmembrane protein, given that both proteins would appear to localize to the plasma membrane? At the resolution used by An et al., it is submitted that such a distinction could not be made with reasonable certainty. The specification provides no factual evidence that suggests that the protein encoded by nucleotide sequences SEQ ID NO: 83 or SEQ ID NO: 85 is a transmembrane protein, as opposed to an intracellular protein that associates with the plasma membrane. The declaration asserts that the protein is accessible to an antibody at the surface of prostate, bladder and breast cancer cells, but provides no factual evidence to support

the assertion. An et al., on the other hand, suggests the protein is not a transmembrane protein, but instead a soluble protein localized primarily to the cytoplasm and nucleus.

The declaration further states the use of conventional confocal fluorescence microscopy limited the ability of An et al. to more specifically characterize the localization of the protein and suggests the specification teaches the use of other methodology that remedies the inadequacy of their earlier methodolgy, so as to have permitted the accurate localization of the protein to outside surface of the plasma membrane. Agreeably, the methodology used by An et al. would not permit one to accurately localize the protein, or a portion thereof, to the outside surface of the cell. As evidenced by, for example, the attached references (i.e., Takizawa et al. (of record) and Maddala et al. (*supra*)), the resolution of the microscopy used by An et al. would not have permitted such a conclusion. However, contrary to the statement by Dr. Veltri, there does not appear to be any disclosure in the instant specification of the use of high-resolution confocal immunofluorescent microscopy to localize the protein. In fact, the words "confocal" and "microscopy" do not appear in the specification. Thus, if any merit of the declaration is extended to the instant application, it is not known to which disclosures in the instant specification Dr. Veltri would have referred as providing remedy to the inadequacy of the methodology used by An et al.

The declaration notes the presence of a *putative* transmembrane domain in the protein and states, "the presence of this putative transmembrane domain indicates that UC28 localized to the cell membrane" (item #6). If the domain is only a *putative* transmembrane domain, it has not yet been determined to *be* a transmembrane domain. The disclosure by An et al. suggests that the protein is not present at the extracellular surface, as if it were, its presence there was unremarkable. An et al. teaches the protein primarily localized to the inside of the cell (i.e., the cytoplasm and the nucleus); the results disclosed by An et al. do not suggest that the protein comprises an extracellular domain, or that at least part of the protein is exposed at the surface of cancer cells.

Applicant has previously referred to Carrol (attached as Exhibit A to the amendment filed April 21, 2005); Carrol has written a commentary addressing the

importance of findings disclosed by Milowsky et al. that an antibody that specifically binds protate-specific membrane antigen (PMSA), which is radiolabeled, can be used to treat patients with prostate cancer. Notably, Carrol comments that the antigen to which the antibody binds is an excellent target because it is not secreted like PSA or PAP. As mentioned in the preceding Office action, An et al. suggests that the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85 (i.e., UROC28) is secreted, as it was detected in serum specimens acquired from patients diagnosed with prostate cancer (see, e.g., page 7018, figure 6). Accordingly, Carrol provides factual evidence that the polypeptide is a less desirable target than PMSA since it is secreted. Furthermore, Carrol emphasizes that the reason that PMSA is an excellent target is that the antibody that recognizes it binds tightly to its extracellular domain, as previous monoclonal antibodies bound to an intracellular domain only accessible in already dead or dying cells. Here, as explained above, it is not known whether the protein comprises an extracellular domain that might serve as the target of an antibody, which is conjugated to a radionuclide. To any extent that Carrol might provide support for Applicant's assertion that the claimed invention can be used without undue and/or unreasonable experimentation, that evidence is merely anecdotal. Again, the antibody or other inhibitor to which the claims are directed cannot effectively bind the protein, if it is present only *within* living cancer cells, and if the protein is secreted, while the antibody or inhibitor could bind the protein, it's binding to the protein will not affect the cancer cells that secreted the protein.

Claims 84 and 93 are directed to antibodies that bind the polypeptide encoded by the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85, which are linked to chemotherapeutic agents. As evidenced by Vitetta et al. (of record), for example, there are well known limitations in the art of antibody-targeted therapeutic regimens; but, as explained in the preceding Office action, if a cancer cell does not express the protein that is specifically bound by the antibody at its surface, the use of a pharmaceutical composition comprising such an antibody will not be effective. The specification provides no guidance as to which chemotherapeutic agents are linked to the antibody, so as to provide the claimed therapeutic effect, but it is aptly noted that many

chemotherapeutic agents, unlike radionuclides, must gain access to the inside of the cell to cause harm to the cell. Generally, an immunoconjugate comprising such a chemotherapeutic agent binds an antigen at the surface of the cell, which is then "internalized" by the cell; however, not all antigens (e.g., receptors) are "internalized" and thus many antigens to not constitute suitable targets for such therapeutic agents. Not only is it not known that the protein encoded by the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85 comprises a suitable extracellular domain, but it is also not known whether the protein is "internalized" by the cell following the binding of an antibody.

Furthermore, as Bodey et al. (of record) teaches, the use of such a pharmaceutical composition may paradoxically serve to select against tumor cells that express the protein, while promoting the growth of tumor cells that do not express the protein. It is here again noted that the specification does not teach the activity or function of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 83 or SEQ ID NO: 85; and moreover, although the gene encoding the polypeptide is over-expressed, it is not known whether the polypeptide plays an essential role in the life of the cancer cell, but if it does not, it follows that the use of the claimed invention may lead only to selection against tumor cells that do not express the polypeptide.

Consequently, even if the activity of the protein were known to be essential to the life of the cancer cell, as evidenced by Gura (of record), for example, the art of anticancer drug discovery is unfortunately hindered by the extreme complexity of the biological system and its inherently unpredictable nature. Consequently an inhibitor of the polypeptide (i.e., a naked antibody or "other inhibitor" of the polypeptide) cannot be recognized or made by routine experimentation alone.

It is further noted that the specification does not actually teach that the polypeptides of SEQ ID NO: 84 and SEQ ID NO: 86, which are encoded by an open reading frame of the polynucleotides of SEQ ID NO: 83 or SEQ ID NO: 85, is over-expressed in cancer cells, compared to normal cells of the same tissue type. Moreover, the specification fails to demonstrate a correlation between the level of mRNA expression and the level of protein expression in cancer cells.

In response, Applicant has argued that An et al. teaches the protein is overexpressed in prostate and breast cancer cells. Indeed, using immunohistochemistry to analyze the expression of the protein in formalin-fixed paraffin sections of prostate and breast tumor specimens, An et al. discloses the level of the protein is increased in the prostate cancer glandular epithelial cells and breast cancer ductal epithelial cells as compared to the corresponding normal cells; see, e.g., page 7017, the paragraph bridging columns 1 and 2. However, Applicant is reminded that supporting documents published after the filing date sought by Applicant cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a).

Furthermore, despite teaching its overexpression in breast and prostate cancer cells, An et al. does not teach whether the protein is overexpressed in bladder cancer cells. Again, as evidenced by Chen et al. (of record), for example, one cannot presume that the amount of protein produced in a cell will mirror the amount of mRNA produced. As explained previously, this fact is so universally accepted, it is mentioned in a textbook (i.e., Genes VI, 1997) (of record).

As explained in the preceding Office action, if the protein is expressed at the surface of cells, and the inhibitor is an antibody, unless the cancer cells, relative to normal cells of the same tissue type, more abundantly express the protein, the antibody will not selectively target cancer cells, but will also undesirably target normal cells. One skilled in the art could therefore not use the claimed invention without first performing an undue and/or unreasonable amount of additional complex experimentation to determine if the protein encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 is over-expressed in bladder cancer cells, compared to normal cells of the same tissue type.

Many additional references are cited in the above rejection of the claims under 35 U.S.C. §112, first paragraph, as failing to meet the written description requirement, which further support the propriety of this ground of rejection.

Applicant's arguments set forth in the amendment filed March 4, 2008, beginning at page 13, have been carefully considered but not found persuasive for these reasons.

In addition, Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a peptide or polypeptide encoded by at least a portion of the nucleotide sequence of SEQ ID NO: 83 or SEQ ID NO: 85 that might be, although not is necessarily expressed by breast, bladder and prostate cancer cells, produce an antibody having the ability to bind to the peptide or polypeptide, and then determine if the antibody is capable of inhibiting the growth or survival of cancer cells expressing the peptide or polypeptide, so as to be used therapeutically in treating cancer; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, although Applicant's arguments traversing this ground of rejection have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence of record indicating that the amount of guidance, direction, and exemplification disclosed in the specification would not have been sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 78, 80-84, 86, 87, and 89-94 are rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-38 and 65-72 of copending Application No. 09/966,762. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are drawn to a method for treating breast, bladder or prostate cancer cells comprising administering an "agent" (e.g., inhibitor), or more particularly an

antibody that binds to a peptide or polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85, which the instant specification discloses is a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 84 and SEQ ID NO: 86.

Claims 1-38 and 65-72 of the copending application are drawn to a method for inhibiting cancer cells in a patient comprising administering to the patient a "UC28 inhibitor", including a polyclonal or monoclonal antibody that binds "UC28".

SEQ ID NO: 84 of the instant application is identical to SEQ ID NO: 2 of the copending application. The protein comprising this amino acid sequence is designated "UC28" by both the instant and copending applications; see, e.g., page 12, lines 24-27 of the copending application; and page 19, line 4, and page 115, lines 11-15 of the instant application.

The claims of the copending application do not explicitly recite that the antibody administered is conjugated or linked to a radionuclide or chemotherapeutic agent; however, the claims of the copending application do explicitly recite that the antibody can be conjugated to a "toxin", which is defined as either a chemotherapeutic agent or a radionuclide (page 89, lines 2 and 3).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's remark set forth in the amendment filed March 4, 2008, at page 22, is acknowledged but this ground of rejection will be maintained until it is appropriately remedied.

Conclusion

14. No claim is allowed.

15. As noted in the Office action mailed November 10, 2005, the art made of record cannot be relied upon but is nonetheless considered pertinent to applicant's disclosure. WO 98/04689 A1 (of record) teaches treating prostate cancer by administering to a patient an antibody that binds to a polypeptide encoded by a gene corresponding to the

human prostate cancer marker UC Band #28 (i.e., SEQ ID NO: 3); see, e.g., page 41, lines 10-17; page 50, lines 1-7; page 113, lines 25-27; and claims 53 and 62.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephen L. Rawlings/

Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

slr
June 13, 2008